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Case Report

Overview and management of the neuroendocrine cancer of the bladder with two cases

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Abstract
Small cell neuroendocrine carcinomas are rare (less than 1%) but rather aggressive tumors of the bladder with poor prognosis. The 5-year survival rate is around 14-16%. In this paper, we present two cases: one male at the age of 73 years and one female at the age of 65 years, who were diagnosed with small cell neuroendocrine tumors as a result of the examination of trans urothelial resection (TUR) material performed in 2019. These aggressive tumors are very rare and require multimodal treatment protocols. There are case series in the literature; these series consist of a limited number of patients.

Keywords
Neuroendocrine; Bladder; Small cell; Rare

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Introduction

Extrapulmonary neuroendocrine tumors are extremely rare, and more than 95% of them arise from the gastrointestinal tract. The second most frequent location is the genitourinary tract, and they most frequently occur in the bladder [1]. Two hypotheses are emphasized for neuroendocrine tumor growth, one of which is that it develops from multipotent undifferentiated stem cells. The coexistence of neuroendocrine carcinomas with other histological subtypes of bladder cancers supports this hypothesis. The other less advocated hypothesis is that it develops through the malignant transformation of neuroendocrine cells in the metaplastic urothelium present in the normal bladder [2-4]. Extrapulmonary neuroendocrine tumors have been described in various organs, including the esophagus, stomach, pancreas, gallbladder, uterus cervix, kidney, bladder, and prostate gland [5]. Neuroendocrine tumors are composed of 4 subgroups according to 2016 WHO classification. These are small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, well-differentiated neuroendocrine carcinoma, and Paraganglioma. The most common type is small cell neuroendocrine carcinoma, and it constitutes less than 1% of all bladder malignancies. The chromosomal changes observed in pulmonary small cell carcinoma at the molecular level are also observed in bladder small cell neuroendocrine carcinoma. It is usually seen in the sixth and seventh decade, the incidence in males is three times as many as in females (age range, 36-85 years). A specific etiological factor has not been identified.

Case Report

Case 1:

In the study, among the cases who were diagnosed with bladder TUR material in Kayseri Training and Research Hospital in 2019, two cases were considered to have primary bladder neuroendocrine carcinoma. We aimed to evaluate the cases in terms of job, gender, clinical symptoms, tumor localization, clinical-stage, metastasis, and differential diagnoses as well as considering the diagnosis they received from excision materials and to present the results in line with the literature.

The first case was a 65-year-old female patient who presented with macroscopic hematuria complaint. She did not have a history of smoking, and no other properties other than diabetes mellitus were observed. In the examinations carried out, her erythrocyte was found to be 91 unit size in urinalysis, glomerular filtration rate (eGFR) was 103 mL/min/1.73 m2, and creatinine level was 0.49 mg/dl on a drip. No reproduction was observed in the urinary culture. In the urinary system USG, a 27 mm echogenic node lesion extending from the bladder left anterolateral wall to the lumen was observed. In cystoscopy, a necrotic papillary tumoral lesion with a large pedicle was observed and TUR-M was performed. The material consisting of tissues in pieces making up a total of 11 cc in volume was sampled to be examined in the pathology clinic. Tumor cells in the resections showed solid growth pattern, were invading muscularis propria, consisted of nest-like structures, had a uniform hyperchromatic nucleus, displayed crushed artifact in places, and had narrow cytoplasm and coarse chromatin (Figure 1A). In immunohistochemical staining, B-catenin, synaptophysin (Figure 3A) were (+) with CD56 (Figure 3B), CK 7 (+), and focal weak (+) with TTF-1. Ki-67 proliferation index was above 80%. In focal areas (at a rate of 10-20%), a high grade in situ and invasive urothelial carcinoma areas were present. The patient underwent radical cystectomy and accompanying total abdominal hysterectomy bilateral salpingooforectomy. When the cystectomy material was examined, a tumoral structure of 4x3x1 cm located on the left side wall of the bladder was observed. The sectional surface of the tumor was gray in color and had medium hardness. Macroscopically, tumors invaded adipose tissue. Microscopically, 30% of the tumor was observed to be composed of large cell neuroendocrine carcinoma (Figure.1B) and 70% was made up of nested variant urothelial carcinoma. Perineural and lymphovascular invasions were observed. Nested variant urothelial carcinoma was composed of tumor cells of urothelial origin which constitute irregular small island or abortive tubules structures (Figure 2) that infiltrate into lamina propria and muscularis propria [6]. In tumor cells, only mild atypia (mild pleomorphism, mildly increased N/C ratios, rarely evident nucleoli, rare mitotic figures) was observed. In nested variant urothelial carcinomas, increased atypia and focal anaplasia can usually be seen along with the increased invasion depth. Concomitant typical urothelial carcinoma is frequent. However, in our case, atypia and typical urothelial components were absent. The large cell NEC component, which formed 30% of the tumor had identical features with cellular properties in TUR material. In immunohistochemical staining, while the diffusion with CK 7, Pan CK, P53, and B-Catenin was (+), and with CK20, GATA3, p-CEA and epithelial membrane antigen (EMA), large cell NEC component it was (-), (+) positive staining was obtained in nested variant areas. Synaptophysin and chromogranin were (+) in tumors with neuroendocrine morphology, while they were (-) in nested variant areas. Ki-67 proliferation index was 80% in neuroendocrine carcinoma, while it was 5-10% nuclear (+) in the nested variant carcinoma component. When the patient's-BSO material was evaluated, a specific feature was not observed.

Case 2:

The other case was a 73-year-old male patient who presented to the hospital with painless, clotted, macroscopic hematuria complaints. In the examination, his erythrocytes in urine were 495 and leukocytes were 23 unit size, bacteria were 35 pieces, glomerular filtration rate (eGFR) was 45 mL/min/1.73 m2 and creatinine level was 1.52 mg/dl. In the urinary system USG and lower abdominal CT, on the right posterolateral wall of the bladder, a 51x37 mm solid lesion covering ureter orifices and tending to overflow out of the bladder was observed. In PET CT, intense hypermetabolic areas compatible with the irregular, restricted implant and metastatic lymph node were observed to be starting from the posterior of the right psoas muscle and filling the internal iliacus, external iliacus, and pararectal areas, extending to the anterior of the rectum. Besides, a nodule sized 13x9 mm in the left lower lobe superior segment in the lung, and a nodule with a diameter of 6 mm in the right lower lobe posterobasal segment were observed. It was recommended to follow nodules in terms of metastasis. In the patient's cystoscopy, the tumor had a wide-based, solid, locally papillary, and necrotic appearance. After TUR-M, the material consisting of a total volume of 12 cc and made up of pink-colored irregular tissues

was sent to the pathology clinic. All the material was sampled and examined. In the microscopic examination, in addition to cells with narrow cytoplasm and coarse chromatin showing solid growth pattern, invasive to muscle tissue, and having a hyperchromatic nucleus, the generalized lymphovascular invasion was observed. In the immunohistochemical staining, (+) staining was obtained with CK 7, B-Catenin, p53, and CD56 and Synaptophysin among neuroendocrine markers. In situ or invasive urothelial carcinoma was not observed. The patient underwent radical cystoprostatectomy. When the material was examined macroscopically, a tumoral structure with broken white color which covered an area of 7x4x1 cm on the front wall of the bladder and invaded almost the entire wall, and a total of 9 lymph nodes with reactive appearance (3 right obturators, 3 left obturators and 3 peri vesical adipose tissues) were observed. No features were observed in the prostate tissue and seminal vesicular. In the resections, the entire tumor cells had identical characters, were uniform, had a high nucleus cytoplasm ratio, and had cytoplasm and coarse chromatin showing crushed artifact in places. Necrosis was observed. Tumor subserosa was invasive into the adipose tissue. Perineural and lymphovascular invasion were observed. When dissected lymph nodes were immunohistochemically evaluated with Pan CK, no tumor was observed.

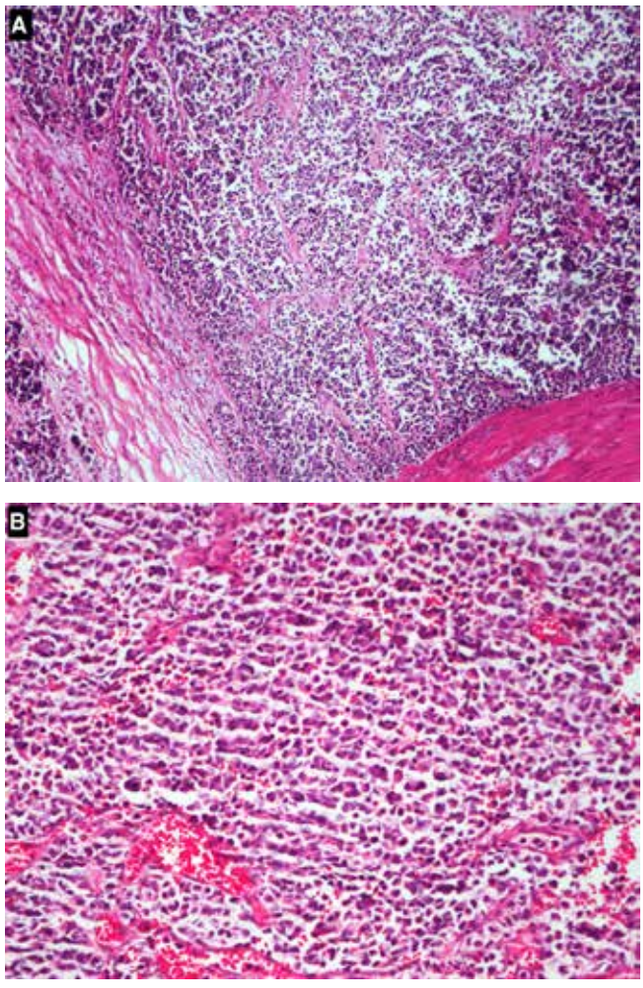

Figure 1. Neuroendocrine carcinoma consists of small, rather uniform cells, with nuclear molding, scant cytoplasm, and nuclei containing finely stippled chromatin and inconspicuous nucleoli.
A: 65-year-old female patient, **B:** 73-year-old male patient (H&E stain, x 100).

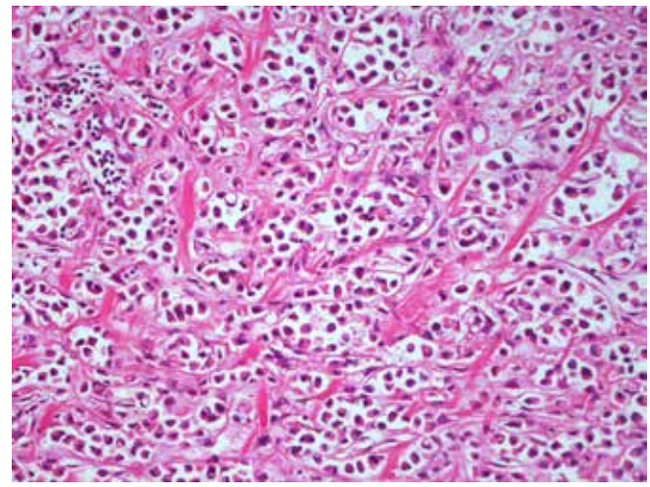

Figure 2. Nested cell variant of urothelial carcinoma of the urinary bladder (H&E stain, x 200).

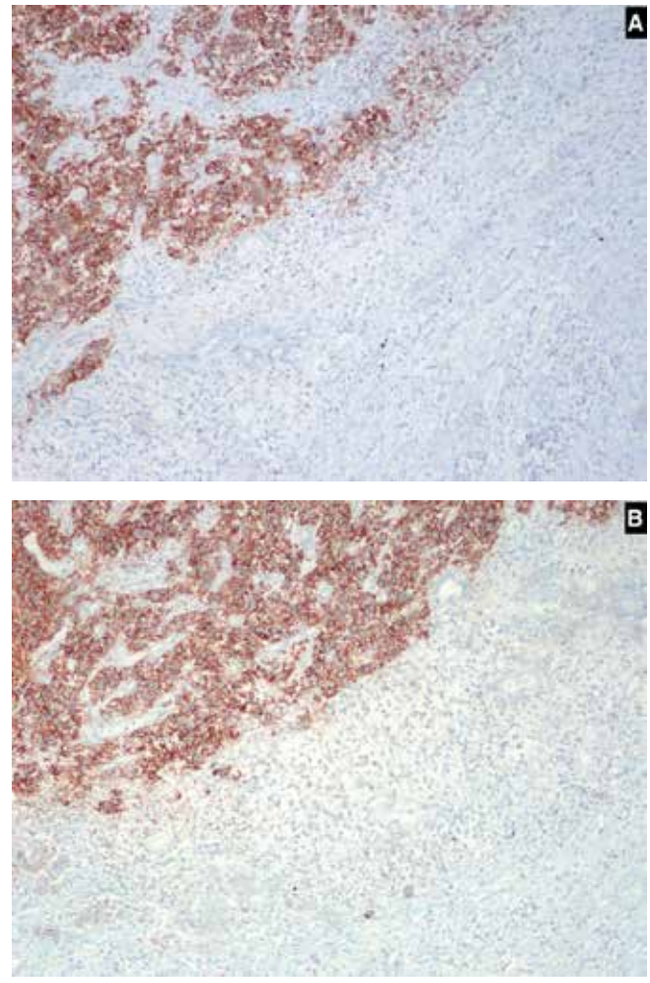

Figure 3. Strong membranous expression of the neuroendocrine marker in a case of neuroendocrine carcinoma; A: Synaptophysin (Synaptophysin, x100), B: CD 56 (CD56, x100).

Discussion

Similar to conventional urothelial carcinoma, frequent symptoms in bladder neuroendocrine carcinoma are dysuria, nocturia, frequent urination, obstructive symptoms, localized abdominal or pelvic pain, and gross hematuria. Systemic symptoms are nonspecific and usually anorexia and weight loss. Smoking history is usually present. In rare cases, hypercalcemia, hyperphosphatasemia, and ACTH ectopic

secretion can be seen paraneoplastically. In our case, both patients presented with hematuria complaints, and there was no apparent paraneoplastic condition. Though regional lymph node metastasis is frequent, bone, lung, and liver metastases can also be seen [3-7]. Brain metastasis of bladder small cell neuroendocrine tumors is less common than brain small cell tumors [8]. Most of the small cell NECs are located mostly in the bladder, and most frequently on the lateral wall and dome. It can also develop in diverticula. Macroscopically, it forms a large, solid, solitary, polypoid, and nodular mass. It can infiltrate into the ulcer, sessile in a prevalent way. When the tumor is diagnosed, it has already infiltrated into muscularis propria. In our case, when the patients were first diagnosed, they had deep muscle layer invasion. The tumor was located in the bladder anterolateral and posterolateral wall, and the tumor had a nodular structure.

Microscopically, it is made up of layers and nest structures which are formed by narrow cytoplasmic cells that are separated by fibrous stroma, that show nuclear molding, that are small to medium-sized and oval round, having no nucleolar prominence, and unclear nuclear detail. A great number of easily noticeable mitosis and nuclear fragmentation are observed. Point or geographic necrosis is prevalent, and the Azzopardi phenomenon, which expresses the typical arrangement of cells, is seen around the vessels. Rarely, tumor badges can be seen. Vascular invasion almost always exists. In addition to small cell morphology that forms most of the tumoral structure, it can include invasive and non-invasive urothelial carcinoma components and other squamous, glandular and sarcomatous differentiation areas and is found in 12-61% of the cases. Among IHC staining, it is stained (+) with synaptophysin, chromogranin, and NSE, but the loss of expression does not rule out the diagnosis. It is specific to TTF-1, thyroid, and lung carcinomas, and at the same time, it is expressed in 40% of the small cell NECs. CK7 is (+) in 60% of patients, CK20 and uroplakin III are negative (-). Immunohistochemical findings in our cases support the neuroendocrine tumor. CD44 can be used in distinguishing between poorly differentiated urothelial carcinoma and small cell NEC. CD44 is one of the transmembrane glycoproteins that enables cell-cell and cell-matrix adhesion. While it is stained by 60% in urothelial carcinoma, the staining rate in small cell NECs is 7%. In both of our cases, (-) result was obtained with CD 44. Tyrosine kinase found in many physiological and pathological processes such as C-kit hematopoiesis and carcinogenesis is an intermediary transmembrane protein. The aberrant signal paths in pulmonary small cell carcinomas can be present in bladder NECs. For example, the C-KIT /stem cell factor pathway frequently identified in pulmonary small cell carcinomas has been detected in 40% of the bladder NECs. In our cases, the female patient showed diffusion with CD117, while the male patient showed focal membranous staining.

In the differential diagnosis, small cell carcinoma metastasis, lymphoma, lymphoepithelioma-like carcinoma, plasmacytoid carcinoma, and poorly differentiated urothelial carcinoma play a role.

Immunohistochemical studies help with the differential diagnosis. If tumor cells form discohesive groups, or if fixation-related artifacts are present, malignant lymphoma may sometimes resemble small cell neuroendocrine carcinoma. In this case, staining features such as (+) with LCA (Leukocyte common antigen), (-) with keratin and neuroendocrine markers, which are not typically expressed in small cell neuroendocrine tumors help in the diagnosis. In our cases, (-) staining was obtained with LCA as well. Similarly, plasmacytoid carcinoma, poorly differentiated urothelial carcinoma, and squamous cell carcinoma do not show expression with neuroendocrine markers such as synaptophysin and chromogranin. It is difficult to distinguish between prostate and bladder neuroendocrine carcinomas in small biopsy materials and molecular studies may be required. For example, TMPRSS2 -ERG gene fusion shows prostate-originated small cell carcinoma.

As a result, these aggressive tumors are very rare and require multimodal treatment protocols. Although there are case series in the literature, these series consist of a limited number of patients. Therefore, standard treatment protocols have not been determined and cystectomy is accepted to be the best treatment protocol following neoadjuvant platinum-based chemotherapy and implemented. Recently, it has been reported that radiotherapy provides equivalent results with radical surgical treatment. Treatment should start quickly and be aggressive. The prognosis depends on the pathological stage. Some studies support treatments aimed at C-kit expression and PDGFRA (platelet-derived growth factor alpha) mutation.

In approximately 40-50% of cases, carcinomas other than small cell ones such as carcinoma in situ, classic urothelial carcinoma, squamous cell carcinoma, adenocarcinoma, and sarcomatous carcinoma are present. The presence of these morphologies does not rule out the diagnosis of small cell carcinoma.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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